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(54) Pharmaceutical compositions and dispensing means.

(57) A solutions of an inhalation medicament is packaged in a sealed dispenser containing a pressurised gas and provided with a one-way outlet valve, eg a metering valve.

The dispenser may be prepared by introducing the solution and the pressurised gas into the dispenser under sterile conditions. Alternatively, the dispenser may be sterilised after introduction of the solution and gas.

After being dispensed from the dispenser, the solution can be administered by nebulisation.

A particularly preferred solution for use in conjunction with the dispensers contains sodium cromoglycate and chlorbutol. This solution is indicated for use in the treatment of reversible obstructive airways disease.

An aqueous solution of sodium cromoglycate and chlorbutol is prepared by dissolving the chlorbutol in distilled water at a temperature of 20-60° C in a covered or sealed vessel and admixing the resulting solution with solid sodium cromoglycate.

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EUROPEAN SEARCH REPORT

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DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	US-A-3 024 787 (H.M. BIRCH) * Column 1, line 61 - column 2, line 10 *	1-7	A 61 M 11/00 B 65 D 83/14 A 61 K 9/00
X	EP-A-0 260 067 (MINNESOTA MINING AND MANUFACTURING CO.) * Column 5, line 60 - column 6, line 6; column 11, line 59 - column 12, line 10 *	1.6.7	
A	US-A-3 985 868 (H.S. COREY) * Column 4, lines 7-9 *	2	
A	US-A-3 131 834 (P. MESHBERG) * Column 1, line 19 *	3	
A	EP-A-0 143 577 (FISONS PLC.) * Page 7, line 12; page 12, lines 5-7 *	5	
A	EP-A-0 274 590 (Dr. GERHARD MANN CHEMOPHARM. FABRIK GmbH) * Claims *	9	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

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The present search report has been drawn up for all claims

Place of search	Date of completion of search	Examiner
The Hague	29 October 90	GERARD B.E.

CATEGORY OF CITED DOCUMENTS

X: particularly relevant if taken alone
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The title of the invention has been amended (Guidelines for Examination in the EPO, A-III, 7.3).

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After being dispensed from the dispenser, the solution can be administered by nebulisation.

A particularly preferred solution for use in conjunction with the dispensers contains sodium cromoglycate and chlorbutol. This solution is indicated for use in the treatment of reversible obstructive airways disease.

An aqueous solution of sodium cromoglycate and chlorbutol is prepared by dissolving the chlorbutol in distilled water at a temperature of 20-60° C in a covered or sealed vessel and admixing the resulting solution with solid sodium cromoglycate.

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Pharmaceutical Compositions

This invention relates to pharmaceutical compositions, in particular compositions for administration by inhalation, packaging therefor, and the use of such compositions in the treatment of reversible obstructive airways disease.

The administration of medicaments by inhalation is well known. Medicaments for administration by the inhalation route are generally formulated either as powders, for administration by insufflation or as pressurised aerosols, or as solutions, eg aqueous solutions, for administration by nebulisation.

Solutions for inhalation may be put up either as single dose or as multi-dose formulations. Both presentations suffer from certain disadvantages. Single dose packaging is less convenient to use and more expensive and wasteful to manufacture. Such packaging frequently takes the form of glass ampoules, each containing a unit dose. Typically, the ampoule is broken open immediately prior to use and the contents transferred to a nebuliser for administration. The breaking open of the ampoule can give rise to the formation of glass sherds which are liable to be inhaled by the patient. This is clearly undesirable. Multi-dose packaging, in which the solution is packaged as a bulk from which unit doses can be dispensed immediately prior to use, is on the face of it much more attractive. However, it has hitherto been found that, in order to maintain the sterility of the solution, the formulation must contain a preservative. This is a serious disadvantage since any preservative used may inter alia adversely affect the stability of the solution or, more seriously, may cause unwanted side-effects. In particular, the preservative generally used, benzalkonium chloride, has been found to have unacceptable sensitising, ie allergic, effects or to have bronchoconstrictor properties when administered directly to the lung.

The present invention overcomes or substantially mitigates the above disadvantages.

According to the invention there is provided a sealed dispenser provided with a one-way outlet valve and containing a pressurised gas and a sterile solution of an inhalation medicament.

The dispenser according to the invention is advantageous in that it provides a relatively inexpensive and convenient form of packaging for multi-dose pharmaceutical solutions. Furthermore, the dispenser enables the storage and multiple dosing of unpreserved solutions of medicament while maintaining adequate sterility. By "adequate sterility" we mean fewer than 50 microorganisms per gram of solution. According to one preferred aspect of the invention there is therefore provided a sealed dispenser provided with a one-way outlet valve and containing a pressurised gas and a sterile unpreserved solution of an inhalation medicament.

Aliquots of the solution contained within the dispenser may be dispensed, eg into a nebuliser for administration to a patient.

The dispenser may be manufactured from any of a number of materials. Suitable materials include, for example, glass and plastics, eg polytetrafluoroethylene. We prefer, however, that the dispenser be manufactured from metal, especially aluminium.

When the dispenser is made of metal the internal surface of the dispenser is preferably lacquered or otherwise coated to prevent or inhibit contamination of the solution with heavy metals.

The pressurised gas may be, for example, any pressurised gas suitable for use as an aerosol propellant. Examples of suitable gases are hydrocarbons, eg butanes and pentanes, nitrous oxide, carbon dioxide and dimethyl ether. We prefer, however, the pressurised gas to be nitrogen.

The dispenser may be pressurised to any pressure sufficient to bring about accurate dispensing of aliquots of solution. The pressure may, for example, be from about 30 to 100 kpa, and is typically from 50 to 80 kPa.

The one-way outlet valve is typically of conventional design and preferably includes a metering chamber. The valve is preferably crimped onto the dispenser and sealed with a gasket, eg a butyl rubber gasket. Where, as is preferred, the valve is a metering valve, the metering volume may typically be from 0.5 to 5ml. For many applications a metering volume of 2ml is appropriate.

The metering chamber of the valve preferably communicates with the interior of the dispenser via an elongate tube extending to a region near the bottom of the dispenser. This has the advantage that the dispenser may be used in the upright position. Alternatively, where no elongate tube is provided, the dispenser may be operated in the inverted position.

The valve is preferably provided with an outlet tube or spout to facilitate transfer of dispensed solution to, for example, a nebuliser.

The inhalation medicament may be of any class of drug conventionally administered by the inhalation route, eg bronchodilators, steroids and anti-allergy drugs, for example drugs which function by preventing or inhibiting the release of factors which mediate the allergic reaction. Specific drugs of the latter category

which may be mentioned include those known by the generic names nedocromil sodium and sodium cromoglycate.

Generally, the solution may be prepared by methods known to be suitable for preparing solutions of the particular inhalation medicament concerned. Similarly, the dispenser may be filled by conventional methods, eg by aseptically introducing the solution into the dispenser and then pressurising under sterile conditions. Alternatively, the sterile solution may be introduced into the dispenser after pressurisation. As a further alternative, the solution and dispenser may be sterilised, eg by gamma irradiation, after filling of the solution into the dispenser and pressurisation.

Although, as noted above, the dispenser according to the invention may eliminate the need for the solution to contain a preservative, a preservative may nonetheless be included in the solution if desired.

A particularly preferred solution for use in conjunction with the dispenser of the invention contains sodium cromoglycate and chlorbutol. This solution is particularly advantageous in that, although it contains a preservative, it can be administered directly to a patient's lung with no significant sensitising or bronchodilatory effect.

The concentration of chlorbutol in the solution should be such that bacterial growth in the formulation is inhibited. We have found that acceptable concentrations of chlorbutol are greater than 0.25% w/v but that the upper limit for the concentration of chlorbutol is about 0.6% w/v.

The concentration of sodium cromoglycate in the solution may be in the range 0.1 to 10%, preferably from 0.5 to 5% and more preferably about 1 or 2% w/v.

Thus, according to a preferred aspect of the invention, there is provided a sealed dispenser provided with a one-way outlet valve and containing a pressurised gas and a sterile aqueous solution comprising 0.1 to 10% w/v sodium cromoglycate and 0.25 to 0.6% w/v chlorbutol.

The solution may also contain an effective proportion of a pharmaceutically acceptable chelating or sequestering agent such as ethylene diamine tetraacetic acid or its salts, eg its disodium salt (disodium edetate).

The concentration of the chelating or sequestering agent should be such as to ensure that no precipitate of metal salts of cromoglycic acid occurs. A suitable concentration may be from 0.01 to 1.0% w/v and preferably from 0.04 to 0.06% w/v, eg 0.05% w/v.

The formulation may also contain buffers, eg sodium dihydrogen orthophosphate (sodium acid phosphate BP), disodium hydrogen phosphate (sodium phosphate BP), sodium citrate/citric acid, and boric acid/sodium borate.

The formulation preferably has a pH in the range 3.0 to 6.0, more preferably 4.0 to 5.0.

The formulation may be made isotonic with physiological fluids by the incorporation of a suitable tonicity agent, eg sodium chloride.

Conventional sterile formulations of sodium cromoglycate are prepared by making a double strength solution of the preservative, eg benzalkonium chloride, and a double strength solution of sodium cromoglycate and mixing the two together. However, we have now found that this conventional method of preparation is not suitable for aqueous solutions of sodium cromoglycate and chlorbutol. Instead, we have found that satisfactory results may be obtained by dissolving chlorbutol in distilled water at a temperature in the range 20-60°C in a sealed or covered vessel and admixing the resulting solution with solid sodium cromoglycate.

We prefer the chlorbutol to be dissolved at a temperature in the range 45-55°C, more preferably at a temperature of about 50°C.

The solution of sodium cromoglycate and chlorbutol is useful, inter alia, in the treatment of reversible obstructive airways disease, including "extrinsic" allergic asthma and "intrinsic" asthma (in which no sensititivity to extrinsic antigen can be demonstrated).

According to another aspect of the invention there is provided the use of sodium cromoglycate and chlorbutol in the manufacture of a medicament for the treatment of reversible obstructive airways disease.

According to another aspect of the invention there is provided a method of treatment of reversible obstructive airways disease, which method comprises administration to a patient suffering from or susceptible to that condition of a therapeutically effective quantity of a solution of sodium cromoglycate and chlorbutol.

An aliquot of solution dispensed from the dispenser may be administered as a nebulised cloud which may be produced by known techniques, eg using a conventional nebuliser.

The dosage to be administered will vary with the particular inhalation medicament used, and with the condition to be treated and its severity. However, in general for sodium cromoglycate a total daily dose of active ingredient in the range 15 to 30mg, eg 20mg, is satisfactory. The total daily dose may be given in 1 to 4 divided doses.

Suitable unit volumes to be administered are in the range 1 to 4ml, eg about 2ml. The unit volume is preferably administered 4 times a day or as required by the patient.

The formulations are preferably packaged in a multidose dispenser containing io to 300ml of solution. We prefer the formulations to be packaged in 60ml, 120ml or 240ml volumes.

The invention is illustrated, but in no way limited, by the following Examples.

Example 1

Formulation 1

Sodium cromoglycate	1.00 % w/v
Chlorbutol	0.50
Disodium edetate	0.05

80ml distilled water was added to 0.5g chlorbutol in a volumetric flask. The flask was sealed and placed in an ultrasonic water bath for one day at a temperature of 25-40.C. 1g sodium cromoglycate and 0.05g disodium edetate were added to this solution and the volume made up to 100ml with distilled water.

Formulation 2

Sodium cromoglycate	1.00 % w/v
Chlorbutol	0.50

This formulation was prepared following the method used for Formulation 1 above.

Stability

Formulations 1 and 2 were stored at 4°C, 25°C and 37°C and analysed at intervals of 1 week, 2 weeks, 4 weeks, 2 months and 3 months using high performance liquid chromatography (HPLC). The formulations were found to be stable at all temperatures and times.

Example 2

Aliquots of a bulk quantity of Formulation 1, prepared as described in Example 1, were sterile-filled into epoxy-lined aluminium cans fitted with metering valves (Lablabo, Montrouge, France) with a 2ml metering volume. Three sizes of can were used with capacities of approximately 60, 120 and 240 ml. The cans were then pressurised with nitrogen gas to a pressure of approximately 70 kPa.

The filled cans were then subjected to a stability test program at 4°C/ambient relative humidity and at 25°C/ambient relative humidity, and 120ml cans were also stored at 40°C/75% relative humidity. Some cans were also cycled between 4°C and 40°C to simulate changes that may be encountered during shipping and handling.

Various parameters were tested prior to storage, including:

1. Appearance/odour
2. pH
3. Microbial count and absence of pathogens
4. Sodium cromoglycate concentration
5. Sodium cromoglycate related substances concentration
6. Chlorbutol concentration
7. Disodium edetate concentration

8. Pressure

The cycled samples, samples stored at 40°C/75%RH for 1, 2 and 3 months and samples stored at 25°C/ambient RH up to 6 months were also tested.

All initial and subsequent test results were within their respective specifications except for the presence of an expected small amount of precipitate in samples stored at 40°C/75%RH after 3 months. This precipitate is probably cromoglycic acid formed as a result of temperature and drop in pH resulting from the breakdown of a small amount of chlorbutol at the high temperature after 3 months storage.

Example 3

An aerosol canister fitted with a metering valve was filled with sterile aqueous 1.0% w/v sodium cromoglycate solution and pressurised with nitrogen gas.

The aerosol canister was stored in the open laboratory for a period of 23 days. Each day a 1g sample of the solution from the canister was weighed into a 10ml aliquot of sterile peptone water, filtered through a sterile membrane filter, washed with 100ml USP phosphate buffer pH 7.2 and transferred onto either tryptone soya agar (for bacteria) or malt extract agar (for yeasts and moulds).

Bacterial plates were incubated at 30°C for 3 days and the fungal plates were incubated at 25°C for 7 days. Following incubation any microorganisms growing on the filters were counted.

The results were as follows:

a) Bacterial contamination

2 bacteria were counted in the sample taken on day 21 and 1 in the sample from day 9. Otherwise no microorganisms were observed.

b) Yeast and Mould contamination

1 microorganism was counted in the samples from day 8, day 21 and day 22. Otherwise no microorganisms were observed.

These results indicate that over the three weeks of testing there was no proliferation of any microorganisms which may have contaminated the sodium cromoglycate solution.

Claims

1. A sealed dispenser provided with a one-way outlet valve and containing a pressurised gas and a sterile solution of an inhalation medicament.

2. A dispenser according to Claim 1, which is manufactured from aluminium lacquered or otherwise coated to prevent or inhibit contamination of the solution.

3. A dispenser according to any one of the preceding claims, wherein the pressurised gas is nitrogen.

4. A dispenser according to any one of the preceding claims, pressurised to a pressure of from 30 to 100 kPa.

5. A dispenser according to any one of the preceding claims, wherein the one-way outlet valve is a metering valve with a metering volume of from 0.5 to 5ml.

6. A dispenser according to any one of the preceding claims, wherein the inhalation medicament is an anti-allergy drug which functions by preventing or inhibiting the release of factors which mediate the allergic reaction.

7. A dispenser according to any one of the preceding claims, wherein the solution is unpreserved.

8. A dispenser according to any one of Claims 1 to 6, wherein the solution comprises 0.1 to 10% w/v sodium cromoglycate and 0.25 to 0.6% w/v chlorbutol.

9. A process for the preparation of a an aqueous solution of sodium cromoglycate and chlorbutol which comprises dissolving chlorbutol in distilled water at a temperature in the range 20-60°C in a sealed or covered vessel and admixing the resulting solution with solid sodium cromoglycate.

10. The use of sodium cromoglycate and chlorbutol in the manufacture of a medicament for the treatment of reversible obstructive airways disease.

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